REMARKS

Entry of the foregoing and favorable reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, and in light of the remarks which follow, are respectfully requested. A two month extension of time is requested to extend the period for filing a reply to the above Office Action.

By the present amendment, claims 1 and 30 to 32 have been amended to correct typographical errors in the chemical names of the buffers and to recite "α_1" and "α_2" instead of "a_1" and "a_2" respectively. Claim 12 has been amended to delete carbonates as the additive. Claim 31 has further been amended to reflect that the method claimed therein comprises analyzing or separating the immunoglobulins already present in the clinical sample. Applicant submits that no new matter has been added via this amendment.

Claims 1 and 30 to 32 have been objected to due to informalities. As mentioned above, these claims have been amended to attend to these informalities. Therefore, this objection should now be rendered moot.

Claim 31 has been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, as set forth on page 3 of the Official Action, it was not clear to the Examiner "how the method comprises analyzing or separating serum protein constituents selected from albumin, a1-globulin, a2-globulin,ß-globulin, $ß_1$-globulin, $ß_2$-globulin and γ-globulin when none of these proteins is positively recited as being introduced in the sample." As stated above, claim 31 has been amended to make clear that the present method comprises analyzing or separating the serum protein constituents of α1-globulin, α2-globulin, ß-globulin, $ß_1$-globulin, $ß_2$-globulin and γ-globulin that are present in the clinical sample, which is introduced into the capillary tube during the "introducing

step." Therefore, a positive recitation of the introduction of these proteins into the capillary tube during the introducing step is unnecessary. Thus, in view of the foregoing, withdrawal of the Section 112, second paragraph rejection is respectfully requested.

Claims 1, 3, 8 to 11, 16 to 19, 21 to 25 and 32 have been rejected under 35 U.S.C. § 103(a) over Keo *et al.* (U.S. Patent 5,599,433) in view of Lehninger I (Principles of Biochemistry pp. 706-707 (1982)) and Lau (U.S. Patent 5,194,390). For the following reasons, however, this rejection is respectfully traversed.

As previously explained in the Amendment dated March 3, 2006, the present invention relates to a method of analyzing or separating protein components from a clinical sample by using an alkaline pH free solution capillary method. This method comprises introducing the clinical sample into a capillary tube containing a buffer system. The buffer system comprises a biological buffer with a pKa at 25°C in the range 8.8 to 10.7 selected from 2-amino-2-methyl-1,3-propanediol (AMPD), N-tris(hydroxymethyl)methyl-4-aminobutanesulphonic acid (TABS), 3-[(1,1-dimethyl-2-hydroxyethyl)amino]-hydroxypropanesulphonic acid (AMPSO), 2-(N-cyclohexylamino)ethanesulphonic acid (CHES), 3-(cyclohexylamino)-2-hydroxy-1-propanesulphonic acid (CAPSO), 2-amino-2-methyl-1-propanol (AMP), 3-cyclohexylamino-1-propanesulphonic acid (CAPS) and 4-(cyclohexylamino)-1-butanesulphonic acid (CABS). Additionally, the buffer system includes at least one additive that increases the ionic strength of the buffer system. This method is used for analyzing or separating serum protein constituents from albumin, α_1-globulin, α_2-globulin, ß-globulin, ß$_1$-globulin, ß$_2$-globulin and γ-globulin.

Meanwhile, Keo *et al.* disclose a buffer and a method useful for the analysis of glycated hemoglobin, *i.e.*, Hb A1c. It was

known in the art that the analysis of Hb A1c or glycated hemoglobin was difficult due to the small differences in isoelectric points between Hb A1c and normal adult hemoglobin (Hb A_o) of 0.1 pH units. Keo *et al.*'s buffer system includes a CAPS buffer, a sugar complexing agent and sufficient sodium hydroxide in the buffer so that it has a pH of about 11 in a capillary electrophoresis method to test for glycated hemoglobin and to distinguish it from normal adult hemoglobin. This patent discloses complexing agents of boric acid, borax, sodium borate or combinations of boric acid and sodium borate. No other sugar complexing agents are disclosed nor exemplified.

Although the Examiner acknowledges that Keo *et al.* does not even mention the recited proteins (*i.e.*, albumin, α_1-globulin, α_2-globulin, ß-globulin, $ß_1$-globulin, $ß_2$-globulin and γ-globulin) that are analyzed and separated by the present method, he nonetheless asserts that Keo *et al.*'s method and buffer system could be used to separate and analyze such proteins, which renders the present method obvious. As support, the Examiner appears to have focused on one section of Keo *et al.* that describes capillary zone electrophoresis (CZE), the electrophoresis technique used in Keo *et al.*, in general terms, and further explains that CZE <u>can</u> be used to analyze serum, plasma and whole blood. Since according to the Examiner, other cited art (namely, Lehninger I and Lau) disclose that the recited proteins are present in serum and plasma, the Examiner concludes that it would have been obvious to use Keo *et al.*'s method and buffer system to separate and analyze the recited proteins. For all the following reasons, Applicant disagrees with this conclusion.

First, the fact that Keo *et al.* <u>could</u> be used in the present method is insufficient as a matter of law to establish obviousness. The question is not whether Keo *et al.*'s teaching <u>could</u> be used, the question is whether or not there is a

teaching or suggestion that such method would be used. The rejection is, by its own admission, a hindsight reconstruction of the invention. Moreover, although Keo *et al.*'s method could use CZE, it is believed to be limited to the measurement or separation of glycated hemoglobin-based proteins, such as Hb A_{1c}, and glycated hemoglobin-based proteins are not found in serum, plasma, urine or cerebral spinal fluid. Indeed, the only exemplary teachings in Keo *et al.* involve the separation of Hb A_{1c} from Hb A_o. Such a separation is the foundation of a clinical assay for the measurement of the amount of glycemia in a patient's blood, which is a hallmark of poorly controlled diabetes. This measurement of Hb A_{1c} gives an indication of the mean plasma glucose level over a period of 120 days; *i.e.*, the life span of erythrocytes or red blood cells. Since this analysis measures glycated hemoglobin, which is found only in erythrocytes, Applicant submits that Keo *et al.* only discloses its method for use in analyzing whole red blood. Therefore, unlike the Examiner's assertion, there is nothing in Keo *et al.* or the other cited art that would suggest that Keo *et al.*'s method or buffer system would be useful for analyzing other clinical samples, such as plasma or serum, other than whole red blood. For example, the clinical sample that is used for Keo *et al.*'s clinical assay is whole red blood, described in Annex I as the lavender top tube which contains EDTA.

Also, there is simply no suggestion in Keo *et al.* that their buffering system can even be applied to separate other proteins other than glycated hemoglobin-based proteins, such as Hb A_{1c} from Hb A_o. For capillary electrophoresis, the particular buffer used impacts the separation of targeted proteins. Buffers are specifically designed to have particular qualities, such as a specific pH, to promote the separation of targeted proteins. As explained above, the Keo *et al.* method and its particular buffer were designed to separate glycated

hemoglobins. Meanwhile, the present invention's method and buffer were designed to separate specific serum protein constituents, namely, albumin, α_1-globulin, α_2-globulin, ß-globulin, $ß_1$-globulin, $ß_2$-globulin and γ-globulin using capillary electrophoresis. Thus, to target the different types of proteins for analysis or separation, one would expect that Keo *et al.*'s buffer to be designed differently (and therefore, have different components and qualities) than the buffer of the method of the present invention. Therefore, a person of ordinary skill in the art would have no reason to guess, let alone expect that Keo *et al.*'s buffer would even be successful or useful in separating or analyzing the above-serum proteins of the present invention.

Indeed, one object of the present invention, as exemplified in claim 32, is to avoid using borate in the buffer of the present method. As explained in the Amendment dated March 3, 2006, borate buffers posed problems because such buffers complexed with glycoproteins, causing the migration of monoclonal proteins with the normal protein fractions. Thus, the normal protein fractions masked certain monoclonal protein peaks. This was especially true of the IgM kappa type monoclonal proteins, whose peaks migrate with the beta-2 fraction when a borate buffer is used. Hence, the present invention solves this problem by using a buffer system without borate. However, as explained in column 5, lines 45 to 48, to achieve its disclosed goal of detecting glycated hemoglobins, Keo *et al.*'s method and buffer system require borate and the complexing of glycoproteins, both of which are not desirable for detecting the recited serum proteins of the present method. Thus, from the foregoing, there is no reasonable expectation of success in using the capillary electrophoresis method and buffer system in Keo *et al.* to separate or detect serum protein constituents in general, let alone the specific serum proteins

of albumin, α_1-globulin, α_2-globulin, ß-globulin, $ß_1$-globulin, $ß_2$-globulin and γ-globulin.

The Examiner has also asserted that any sugar complexing agent can be used in Keo *et al.*'s buffer in view of Keo *et al.*'s disclosure. However, Applicant submits that a person skilled in the art would not use a complexing agent other than borate for Keo *et al.*'s buffer since it is known that borates form stable complexes with sugar residues on glycated hemoglobins, as well as add a negative charge to the glycated hemoglobin. As a result, the glycated hemoglobin's electrophoretic mobility is modified, with the glycated hemoglobin eluting as a later peak than hemoglobin. Since no other sugar complexing agents are mentioned at all in Keo *et al.* and borate is effective for forming stable complexes with sugar residues on glycated hemoglobins, there is nothing in Keo *et al.* that would motivate one of ordinary skill in the art to select a different additive. Additionally, there is nothing in Keo *et al.* that would suggest to one of ordinary skill that the use of any other sugar complexing agent would even be successful or useful in its method and buffer system.

Thus, Keo *et al.* do not disclose or suggest the use of its buffer system for separating or analyzing the serum protein constituents of albumin, α_1-globulin, α_2-globulin, β-globulin β_1-globulin, β_2-globulin and γ-globulin.

Similar arguments to those above were made in the Amendment dated March 3, 2006. However, on page 13 of the Official Action, the Examiner dismissed them with the following assertion:

> Applicant cites col. 5, lines 18-21, of Keo et al and argues that Keo et al is strictly limited to using its buffer system for facilitating the separation of glycoproteins such as HB Alc from other sample constituents. Applicant argues that there is no disclosure in Keo et al that its

> method would be able to separate albumin, α_1-globulin, α_2-globulin, ß-globulin, $ß_1$-globulin, $ß_2$-globulin and γ-globulin. However, this argument is not deemed to be persuasive. First, the recitation "for analyzing or separating" at line 2 in each of claims 1, 31 and 32, and the recitation "for analyzing" at line 2 of claim 30 is merely intended use of the method and is not deemed to be a positive limitation of the claims.

Here, the Examiner is not giving the recited preamble any patentable weight. However, the instant preamble does not merely state a desired effect, but recites an intentional purpose, to analyze and separate a clinical sample comprising specified serum protein constituents. Accordingly, as recognized in MPEP § 2111.02 and case law, such a preamble must be accorded patentable weight. *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333-34, 68 USPQ2d 1154, 1158 (Fed. Cir. 2003) (In a claim directed to a method of treating or preventing pernicious anemia in humans by administering a certain vitamin preparation to "a human in need thereof," the court held that the preamble is not merely a statement of effect that may or may not be desired or appreciated, but rather is a statement of the intentional purpose for which the method must be performed. Thus the claim is properly interpreted to mean that the vitamin preparation must be administered to a human with a recognized need to treat or prevent pernicious anemia.).

In addition, on page 13, the Examiner concluded that even if the preamble were given patentable weight, Keo *et al.* still "analyze or separate a clinical sample comprising serum protein constituents selected form [sic] the recited protein constituents." As support, the Examiner states that "[f]or example, Keo *et al.*'s plasma sample, which contains the instant samples, is analyzed for glycoprotein, and the glycoproteins are separated from other proteins in the clinical sample." However,

as explained above, this reasoning is flawed since there is no disclosure or suggestion that Keo *et al.*'s method be used to separate or analyze any protein other than glycated hemoglobins. As stated above, the only exemplary use disclosed in Keo *et al.* for its method is Hb A_{1c} detection, and Hb A_{1c} detection involves measuring the blood glucose concentration during the lifespan of circulating red blood cells. Thus, the clinical sample in Keo *et al.* must be red blood cells or erythrocytes. Accordingly, Keo *et al.* do not suggest that the protein constituents of albumin, α_1-globulin, α_2-globulin, ß-globulin, $ß_1$-globulin, $ß_2$-globulin and γ-globulin are inherently separated by Keo *et al.*'s method because these constituents are not found in red blood cells.

On page 19, the PTO even went so far as to claim that "the term 'separating' set forth in the instant claims it [sic] so broad that it can be interpreted to mean what Keo et al is doing, *i.e.*, separating the albumin, α_1-globulin, α_2-globulin, ß-globulin, ß-globulins, and γ-globulins that are in the plasma from the glycoproteins so that the glycoproteins can be analyzed." However, regardless of the scope of the term "separating", Keo *et al.* still does not disclose or suggest the separation of serum protein constituents, whether it is from each other or other glycoproteins, because, Keo *et al.*'s method and buffer, as disclosed in Keo *et al.*, is limited to the utility of separating Hb A_{1c} from Hb A_o. As explained above, there is simply no disclosure or suggestion in Keo et al. that its method be used to separate or analyze any other protein besides a glycated hemoglobin.

The secondary references serve only to confirm Applicant's foregoing position. Lehninger I, discloses that plasma does not contain erythrocytes. The secondary reference of Lau *et al.* is directed to a composition for the assay of albumin, which can be found in the urine. However, as stated above, a skilled artisan

would not use clinical samples of plasma or urine to assay glycated hemoglobins, such as HbA_{1c}, since they are found in erythrocytes, and not in plasma or urine. These references, are therefore, non-combinable. Indeed, in column 8, lines 5-15, of Keo *et al.* teaches removing plasma to obtain a clinical sample of red blood cells prior to subjecting the sample to capillary electrophoresis.

Moreover, even if it were proper to combine these references, the combination of the foregoing references fails to render the presently claimed invention obvious since none of the cited prior art references, either alone or in combination, suggest a capillary electrophoresis method to separate protein constituents of albumin, α_1-globulin, α_2-globulin, ß-globulin, $ß_1$-globulin, $ß_2$-globulin and γ-globulin using the particularly claimed buffers and additives.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Claims 2 and 31 have been rejected under 35 U.S.C. § 103 (a) over Keo *et al.* in view of Lehninger and Lau, and further in view of Krylov *et al.*, "Capillary Electrophoresis for the Analysis of Biopolymers," Anal. Chem. Pages 111R-128R (2000). For the following reasons, however, this rejection is respectfully traversed.

Keo *et al.*, Lehninger I and Lau were discussed above and the same arguments are incorporated herein by reference. More specifically, the primary reference of Keo *et al.* does not disclose or suggest using a method to detect albumin or α_1-globulin, α_2-globulin, ß-globulin, $ß_1$-globulin, $ß_2$-globulin and γ-globulin in a clinical sample using capillary electrophoresis. Nor does the method of Keo *et al.* inherently separate these proteins. Keo *et al.* requires borate in their buffer, while the present invention lacks borate in the buffer system.

The secondary references of Lehninger and Lau do not remedy the deficiencies of the primary reference since neither reference discloses a method for analyzing or separating from a clinical sample the serum proteins set forth above using capillary electrophoresis.

Krylov *et al.* describes the analysis of biopolymers and detection of proteins by UV detection. However, Krylov *et al.* also does not remedy the deficiencies of the above-cited references. Even though this reference discloses that human plasma proteins can be separated by CZE, it does not disclose or suggest the use of any other buffer than borate buffer.

Therefore, although it teaches the use of capillary electrophoresis, Krylov *et al.*, even if combined with Keo *et al.*, Lehninger I and Lau, does not remedy the deficiencies of Keo *et al.* for at least the reason that it also does not disclose or suggest a method for analyzing or separating from a clinical sample the serum proteins set forth above using the buffer system recited in claims 1 and 31.

Thus, in view of the above, withdrawal of this rejection is respectfully requested.

Claims 12 to 14 and 30 have been rejected under 35 U.S.C. § 103 (a) over Keo *et al.* in view of Lehninger I and Lau, and further in view of Swank *et al.*, (U.S. Patent 4,810,657). For the following reasons, however, this rejection is respectfully traversed.

Keo et al, Lehninger and Lau were discussed above and the same arguments are incorporated herein by reference, to avoid unnecessary repetition.

Swank *et al.* describe a method of diagnosing multiple sclerosis by noting the streaming potential characteristics of a surface coated with the blood plasma protein of a patient.

On page 7 of the Official Action, the Examiner acknowledges that Keo *et al.* does not specifically teach the presence of

sodium chloride in its buffer system." Nonetheless, the Examiner purports that "[i]t would have been obvious at the time the invention was made to have sodium chloride present in Keo *et al*'s buffer because when Keo *et al*'s capillary zone electrophoresis is performed on blood plasma, sodium chloride will be introduced into the buffer from the blood plasma, which contains sodium chloride, as taught by Swank *et al*."

Irrespective of whether or not Swank *et al*. teaches that plasma contains sodium chloride and introduces it into a buffer during CZE, as explained above, one of ordinary skill in the art would not use the method of Keo *et al*. to analyze a plasma sample since Keo *et al*.'s method is directed to separating glycated hemoglobin, which requires red blood cells as the clinical sample instead of plasma. Accordingly, even if plasma contains sodium chloride, there is no disclosure, suggestion or teaching to use plasma as a clinical sample in Keo *et al*.'s method. Therefore, the combination of cited prior art fails to render the presently claimed invention obvious since none of the prior art discloses or suggests a method to separate protein constituents of albumin, α_1-globulin, α_2-globulin, ß-globulin, $ß_1$-globulin, $ß_2$-globulin and γ-globulin using the particularly claimed buffers and additive by capillary electrophoresis.

Additionally, claims 12-14 and 30 are directed to additives (or their properties) and not to a substance already present in the clinical sample. By definition, an additive is a substance added to improve something. A substance already present in the clinical sample, such as sodium chloride in plasma, cannot be considered an additive since it is not added to the sample to be analyzed. Additionally, claims 12 and 13 are directed to an alkali metal salt additive, which is not the same as sodium chloride although both are salts.

Thus, in view of the above, withdrawal of this rejection is respectfully requested.

Claims 12 to 15 and 30 have been rejected under 35 U.S.C. § 103 (a) over Keo *et al.* in view of Lehninger I and Lau, and further in view of Lehninger II (Principles of Biochemistry, p. 703 (1982)). For the following reasons, however, this rejection is respectfully traversed.

Keo *et al.*, Lehninger I and Lau were discussed above and the same arguments are incorporated herein by reference, to avoid unnecessary repetition.

Lehninger II is from a chapter entitled "Digestion Transport and Integration of Metabolism" and discusses the fact that kidneys use ATP to do osmotic work. Although Lehninger II, in Table 24-2, discloses that sodium sulfate is present in urine, claims 12 to 15 are directed to additives. By definition, an additive is a substance added to improve something. A substance already present in the clinical sample, such as sodium sulfate in urine, cannot be considered an additive since it is not added to the sample to be analyzed.

More importantly, as discussed above, Keo *et al.* cannot use urine as a clinical sample in their method, which utilizes capillary electrophoresis, since the focus of Keo *et al.*'s method is glycated hemoglobin analysis. Such analysis requires the clinical sample to be erythrocytes, and not urine, in order to measure glycated hemoglobin to test for glycemia. Accordingly, even if urine contains sodium sulfate, there is no disclosure, suggestion or teaching to use urine as a clinical sample in Keo *et al.*'s method. Therefore, the combination of cited prior art fails to render the presently claimed invention obvious since none of the prior art discloses or suggests a method to separate protein constituents of albumin, α_1-globulin, α_2-globulin, ß-globulin, $ß_1$-globulin, $ß_2$-globulin and γ-globulin using the particularly claimed buffers and additive by capillary electrophoresis.

Thus, in view of the above, withdrawal of this rejection is respectfully requested.

Claims 1, 3, 8-14, 16 to 25, 30 and 32 have been rejected under 35 U.S.C. § 103 (a) over Keo *et al.* in view of Lehninger I and Lau and Jones *et al.* (U.S. Patent 5,366,601). For the following reasons, however, this rejection is respectfully traversed.

Keo *et al.*, Lehninger I and Lau were discussed above and the same arguments are incorporated herein by reference, to avoid unnecessary repetition.

Jones *et al.* disclose a technique for separating, identifying and measuring ions in solution by CZE, which provides improved sensitivity and resolution of anionic species. Indeed, this patent teaches that sodium octanesulfonate can exhibit lower ionic mobilities in comparison with the UV-absorbing anion in the carrier electrolyte and can be used as an additive for electromigrative trace enrichment with the UV-absorbing anions in the carrier electrolyte. However, Jones *et al.* does not disclose that octanesulfonate can be used in a process other than with ionic molecules. An additive that helps move ions does not necessarily help move serum proteins, and there is no suggestion or teaching in this case that would indicate otherwise. Therefore, Jones *et al.* does not suggest that sodium octanesulfonate can be used in capillary electrophoresis to separate serum proteins, as presently claimed.

The combination of the cited prior art references in this rejection fails to render the present invention obvious since none of these references discloses or suggests a method to separate protein constituents of albumin, α_1-globulin, α_2-globulin, ß-globulin, $ß_1$-globulin, $ß_2$-globulin and γ-globulin using the particularly claimed buffers and additive by capillary electrophoresis.

Therefore, withdrawal of this rejection is respectfully requested.

Claim 2 and 31 have been rejected under 35 U.S.C. § 103 (a) over Keo *et al.* in view of Lehninger I, Lau and Jones *et al.*, and further in view of Krylov *et al.* For the following reasons, however, this rejection is respectfully traversed.

Keo *et al.*, Lehninger, Lau and Jones *et al.* were discussed above and the same arguments are incorporated herein by reference, to avoid unnecessary repetition.

As stated above, Jones *et al.* do not suggest that sodium octanesulfonate can be used to separate serum proteins. The only use for this chemical is as an additive for electromigrative trace enrichment with the UV-absorbing anions in the carrier electrolyte.

Krylov *et al.* disclose that UV absorption can detect plasma proteins when using a borate buffer.

There is simply no suggestion in the combination of these cited references of a method to separate protein constituents of albumin, α_1-globulin, α_2-globulin, ß-globulin, $ß_1$-globulin, $ß_2$-globulin and γ-globulin using the particularly claimed buffers and additive by capillary electrophoresis.

Moreover, it is apparent that the Examiner has not read these references as a whole but has relied on only narrow teachings thereof with the present invention in mind. In this regard, the Examiner is picking and choosing among these references to arrive at the method of the present invention, which amounts to impermissible hindsight reconstruction. See, *Sensonics, Inc. v. Aerosonic Corp.*, 81F.3d 1566, 1570, 38 USPQ2d 1551, 1554 (Fed. Cir. 1996).

Thus, in view of the above, withdrawal of this rejection is respectfully requested.

Claims 1 to 3, 8 to 28 and 30 have been provisionally rejected under the judicially created doctrine of

obviousness-type double patenting as being unpatentable over claims 1 to 5, 7 to 25, 27 to 30 and 33 of copending U.S. Application No. 10/052,931.

Applicant acknowledges that this rejection is provisional and requests that this rejection be held in abeyance until one of these patent applications is allowed.

From the foregoing, favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he telephone Applicants' attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

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Respectfully submitted,

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